

Figure 1

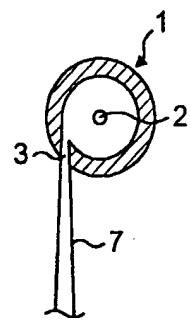


FIG. 2

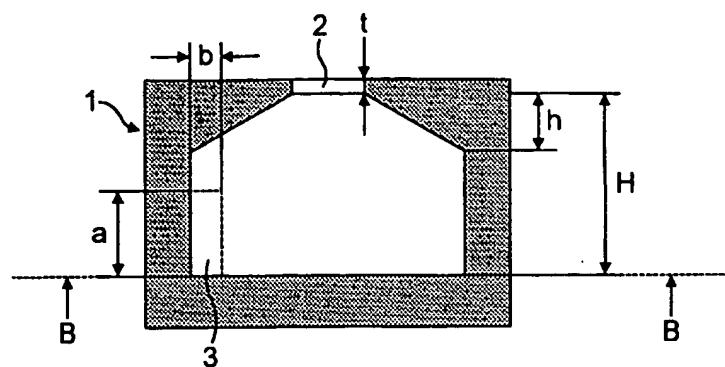


FIG. 3

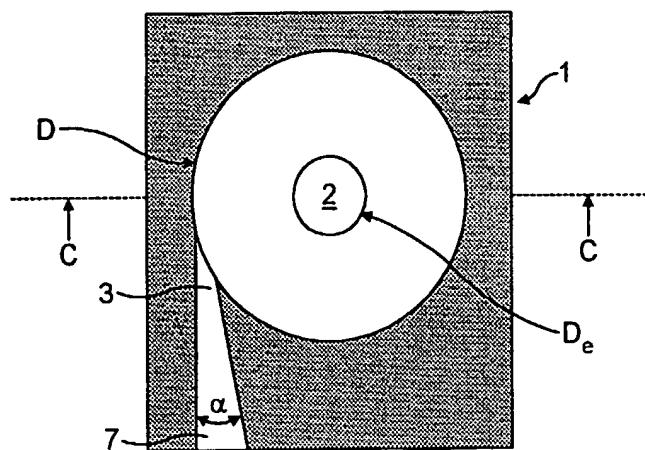


FIG. 4

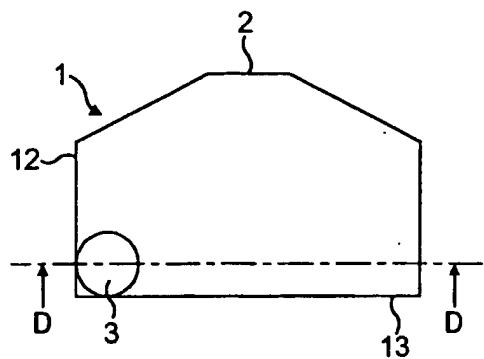


Figure 5a

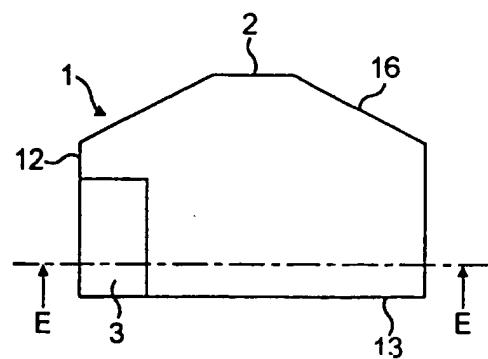


Figure 6a

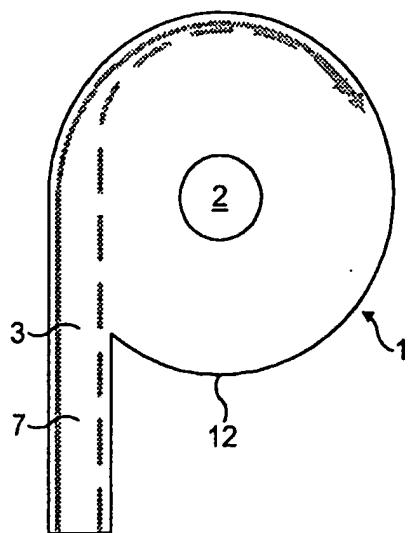


Figure 5b

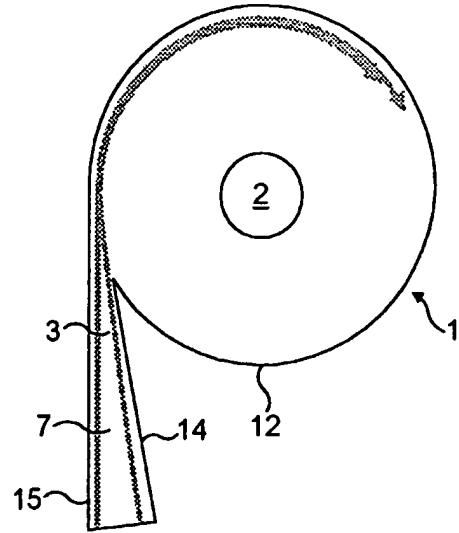


Figure 6b

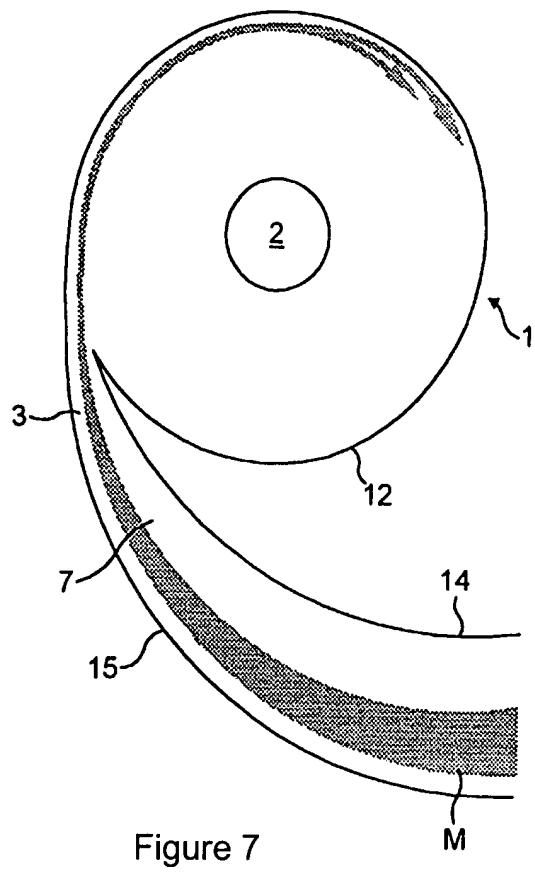


Figure 7

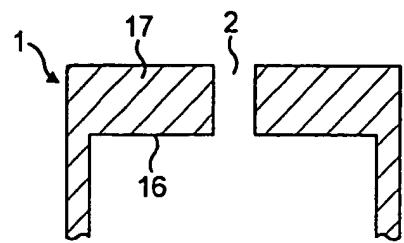


Figure 8

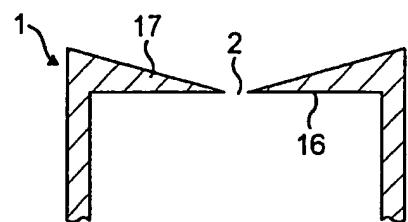


Figure 9

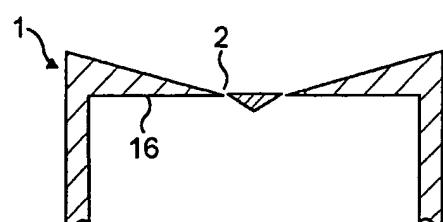


Figure 10

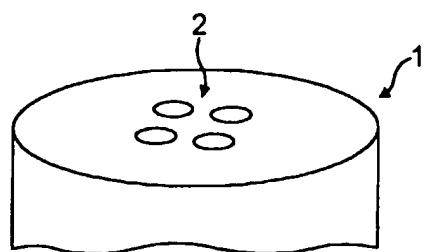


Figure 11

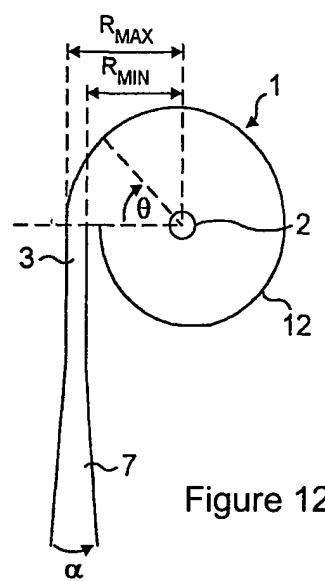


Figure 12

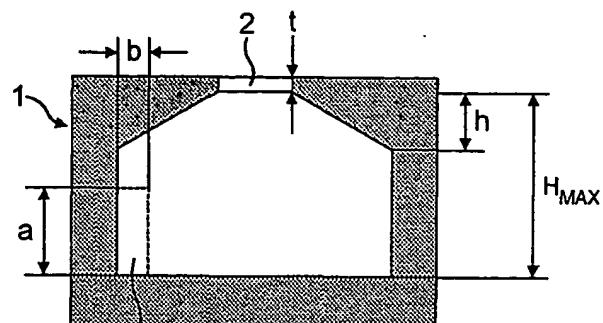


Figure 13

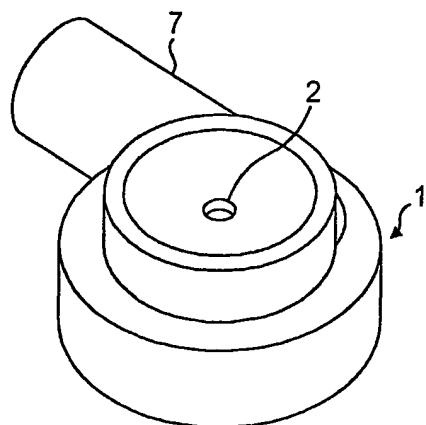


Figure 14

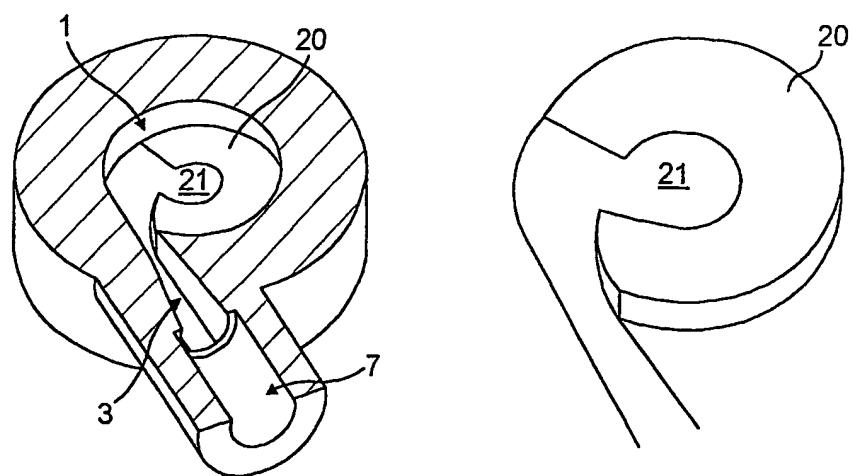


Figure 15

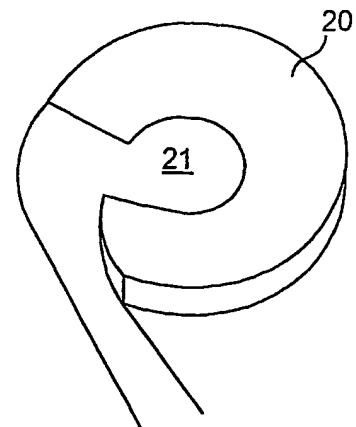


Figure 16

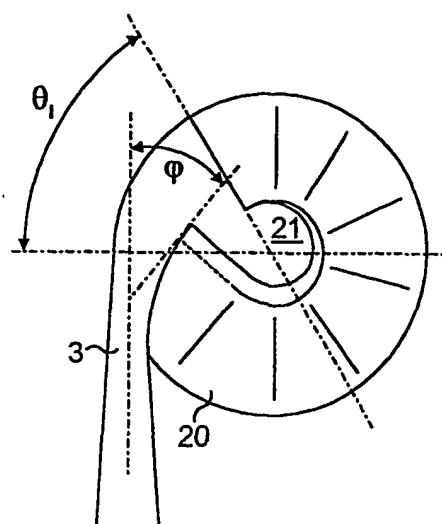


Figure 17

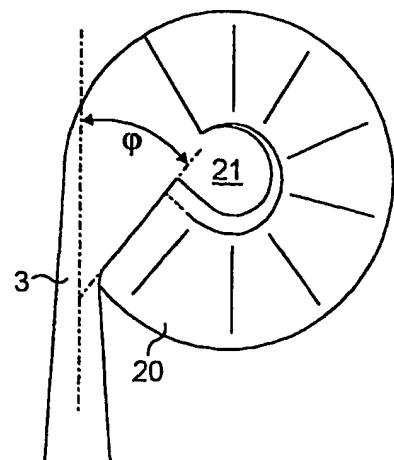


Figure 18

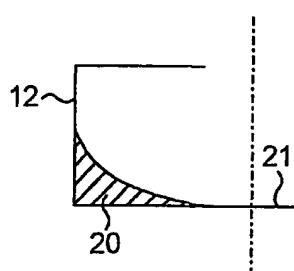


Figure 19

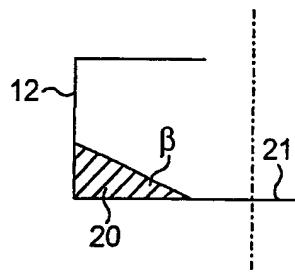


Figure 20

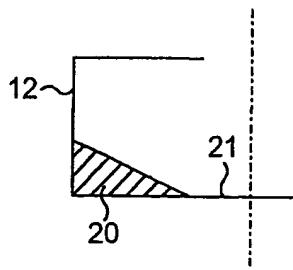


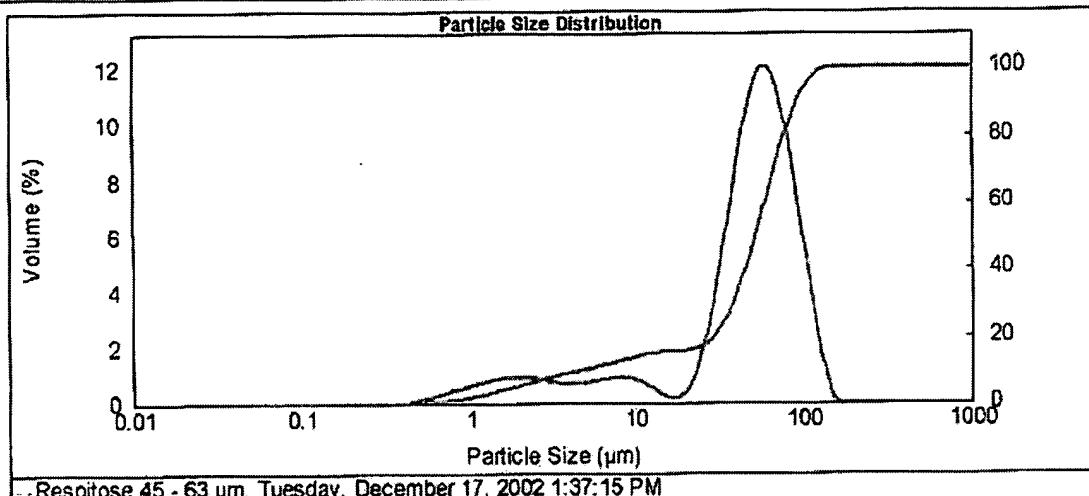
Figure 21

# MASTERSIZER 2000

## Result Analysis Report

Sample Name:  
Respitose 45 - 63  $\mu\text{m}$

Particle Name:	Lactose	Accessory Name:	Hydro 2000SM (A)	Obscuration:	10.11	%
Particle RI:	1.347	Absorption:	0.1	Analysis model:	General purpose	Obscuration (blue): 6.69 %
Dispersant:	Cyclohexane	Dispersant RI:	1.426		Weighted Residual:	0.922 %
Vol. Weighted Mean D[4.3]:	53.494 $\mu\text{m}$	Mode:	59.194 $\mu\text{m}$	Specific Surface Area:	0.504 $\text{m}^2/\text{g}$	
Surface Weighted Mean D[3.2]:	11.916 $\mu\text{m}$	Span :	1.676	Concentration:	0.0247 %Vol	
Result units:	Volume	Uniformity:	0.462			
D(0.1):	5.203 $\mu\text{m}$	d(0.5):	52.769 $\mu\text{m}$	D(0.60):	59.94 $\mu\text{m}$	d(0.9): 93.671 $\mu\text{m}$



Respitose 45 - 63  $\mu\text{m}$ , Tuesday, December 17, 2002 1:37:15 PM

Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %
0.010	0.00	0.105	0.00	1.056	1.68	11.402	14.27	120.226	98.02
0.011	0.00	0.120	0.00	1.259	2.52	13.183	14.76	136.003	99.69
0.013	0.00	0.138	0.00	1.485	3.23	15.135	15.03	158.489	100.00
0.015	0.00	0.158	0.00	1.690	4.02	17.378	15.19	181.970	100.00
0.017	0.00	0.183	0.00	1.905	4.84	19.663	15.37	203.500	100.00
0.020	0.00	0.209	0.00	2.118	5.67	22.909	15.93	228.283	100.00
0.023	0.00	0.240	0.00	2.512	6.48	28.303	17.32	275.423	100.00
0.026	0.00	0.275	0.00	2.884	7.24	30.200	20.04	314.226	100.00
0.030	0.00	0.315	0.00	3.311	7.93	34.574	24.54	365.073	100.00
0.035	0.00	0.363	0.00	3.802	8.57	39.811	31.07	416.639	100.00
0.040	0.00	0.417	0.00	4.365	9.19	45.709	39.55	478.630	100.00
0.046	0.00	0.479	0.00	5.012	9.82	52.481	49.58	542.541	100.00
0.052	0.00	0.560	0.09	5.751	10.49	59.236	62.42	632.957	100.00
0.060	0.00	0.631	0.25	6.607	11.22	69.183	71.13	724.436	100.00
0.070	0.00	0.724	0.53	7.536	12.01	79.420	80.81	831.764	100.00
0.079	0.00	0.832	0.89	8.710	12.82	91.201	88.71	954.903	100.00
0.089	0.00	0.966	1.34	10.000	13.60	104.713	94.47	1098.478	100.00
100.000									

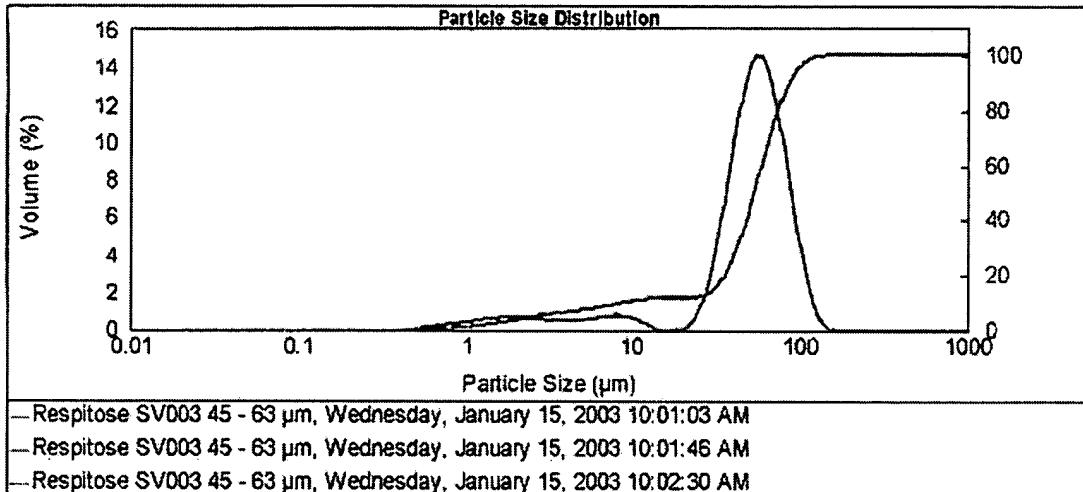
Figure 22(a)

# MASTERSIZER 2000

## Result Analysis Report

Sample Name:  
Respitose SV003 45 - 63 µm

Particle Name:	Lactose	Accessory Name:	Hydro 2000SM (A)	Obscuration:	12.22	%
Particle RI:	1.347	Absorption:	0.1	Analysis model:	General purpose	Obscuration (blue):
Dispersant:	Cyclohexane	Dispersant RI:	1.426		Weighted Residual:	0.627
Vol. Weighted Mean D[4,3]:	53.816 µm	Mode:	57.308 µm	Specific Surface Area:	0.41	m <sup>2</sup> /g
Surface Weighted Mean D[3,2]:	14.626 µm	Span :	1.464	Concentration:	0.0361	%Vol
Result units:	Volume	Uniformity:	0.384			
d(0.1):	8.571 µm	d(0.5):	53.682 µm	D(0.60):	59.54 µm	d(0.9): 67.148 µm

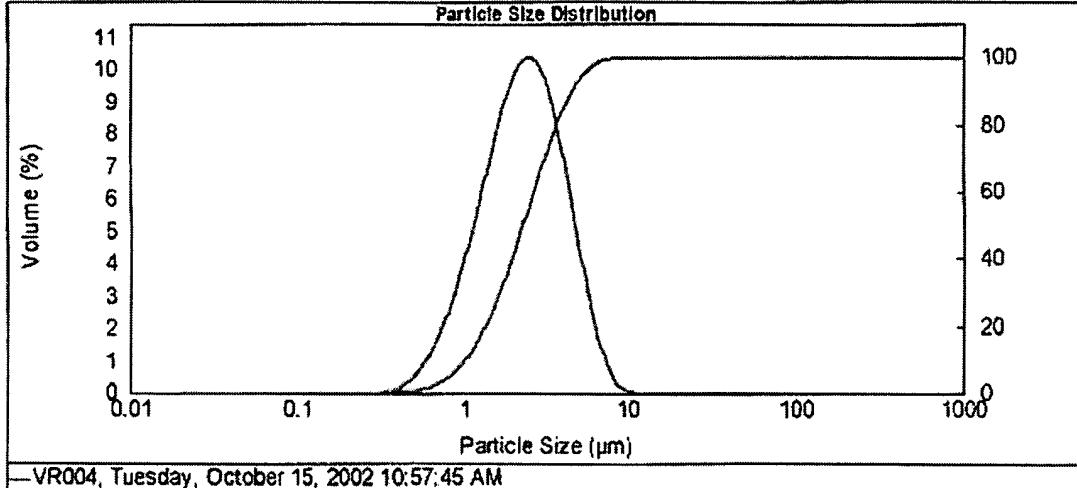


Size (µm)	Vol Under %								
0.010	0.00	0.105	0.00	1.068	1.40	11.482	11.77	120.226	99.21
0.011	0.00	0.120	0.00	1.259	1.08	13.183	11.57	131.038	99.94
0.013	0.00	0.138	0.00	1.445	2.14	15.196	11.60	153.435	100.00
0.015	0.00	0.156	0.00	1.630	3.05	17.318	11.60	181.970	100.00
0.017	0.00	0.162	0.00	1.905	3.70	19.953	11.60	208.930	100.00
0.020	0.00	0.200	0.00	2.168	4.35	22.009	11.73	239.885	100.00
0.023	0.00	0.240	0.00	2.912	4.98	25.303	12.47	295.425	100.00
0.025	0.00	0.275	0.00	2.864	5.55	30.200	14.50	316.226	100.00
0.030	0.00	0.316	0.00	3.311	6.07	34.074	16.68	333.076	100.00
0.035	0.00	0.363	0.00	3.602	6.54	39.811	25.86	416.859	100.00
0.040	0.00	0.417	0.00	4.355	7.01	45.709	35.59	478.830	100.00
0.045	0.00	0.479	0.00	5.012	7.50	52.481	47.85	546.543	100.00
0.052	0.00	0.550	0.00	5.754	8.04	60.226	61.15	630.567	100.00
0.060	0.00	0.631	0.10	6.607	8.67	69.183	73.85	724.436	100.00
0.075	0.00	0.724	0.38	7.568	9.38	79.433	84.46	801.764	100.00
0.090	0.00	0.832	0.66	8.710	10.08	91.201	92.19	964.993	100.00
0.091	0.00	0.855	0.90	10.000	10.75	104.713	98.92	1098.476	100.00

Figure 22(b)

## Result Analysis Report

Particle Name: VR004	Accessory Name: Hydro 2000SM (A)	Obscuration:	15.83	%
Particle 3.000 Absorption: 0.05	Analysis model: General purpose	Obscuration (blue):	15.22	%
Dispersant: Cyclohexane	Dispersant RI: 1.426	Weighted Residual:	0.752	%
Vol. Weighted Mean D[4,3]: 2.587 $\mu\text{m}$	Mode: 2.468 $\mu\text{m}$	Specific Surface Area:	3.19	$\text{m}^2/\text{g}$
Surface Weighted Mean D[3,2]: 1.880 $\mu\text{m}$	Span : 1.539	Concentration:	0.0038	%Vol
Result units: Volume	Uniformity: 0.479			
d(0.1): 1.032 $\mu\text{m}$	d(0.5): 2.290 $\mu\text{m}$	D(0.60) : 2.65 $\mu\text{m}$	d(0.9): 4.557 $\mu\text{m}$	



—VR004, Tuesday, October 15, 2002 10:57:45 AM

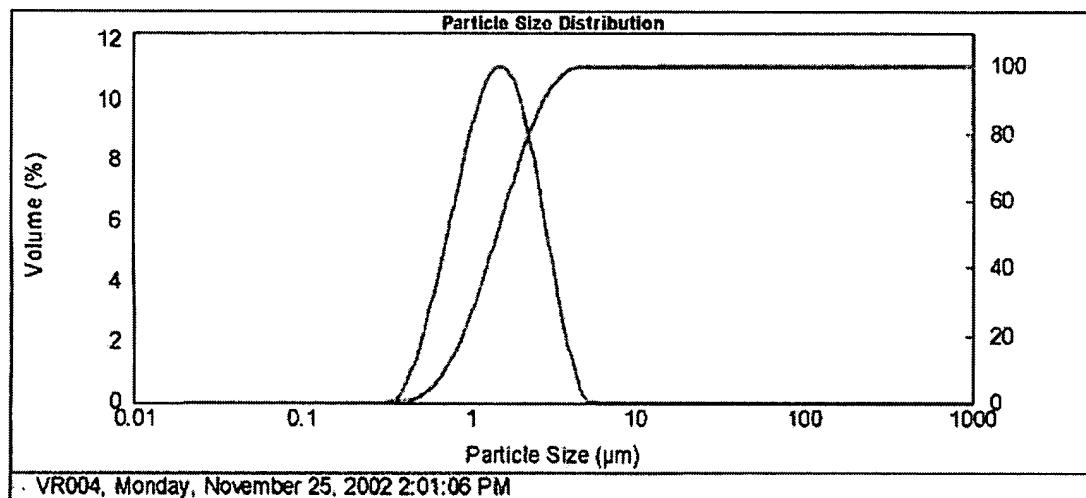
Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %
0.010	0.00	0.105	0.00	1.000	11.78	11.402	100.00	120.226	100.00
0.011	0.00	0.120	0.00	1.250	16.51	13.103	100.00	138.038	100.00
0.013	0.00	0.135	0.00	1.445	22.84	15.130	100.00	150.488	100.00
0.015	0.00	0.158	0.00	1.600	29.03	17.378	100.00	181.970	100.00
0.017	0.00	0.187	0.00	1.905	37.00	19.863	100.00	209.920	100.00
0.020	0.00	0.220	0.00	2.188	49.06	22.909	100.00	239.983	100.00
0.023	0.00	0.240	0.00	2.512	55.28	26.303	100.00	275.423	100.00
0.028	0.00	0.275	0.00	2.854	65.57	30.200	100.00	316.228	100.00
0.030	0.00	0.318	0.00	3.311	74.29	34.874	100.00	363.078	100.00
0.035	0.00	0.363	0.00	3.802	82.00	39.211	100.00	418.869	100.00
0.040	0.00	0.417	0.00	4.365	88.34	45.729	100.00	476.630	100.00
0.045	0.00	0.478	0.00	5.012	93.15	52.465	100.00	540.541	100.00
0.052	0.00	0.560	0.00	5.754	96.46	60.256	100.00	600.957	100.00
0.060	0.00	0.631	0.00	6.607	98.48	69.183	100.00	724.436	100.00
0.068	0.00	0.724	0.00	7.599	99.52	79.430	100.00	831.764	100.00
0.076	0.00	0.832	0.00	8.710	99.92	91.201	100.00	934.983	100.00
0.091	0.00	0.955	7.98	10.000	100.00	104.713	100.00	1038.478	100.00

Figure 23(a)

# MASTERSIZER 2000

## Result Analysis Report

Particle Name:	VR004	Accessory Name:	Hydro 2000SM (A)	Obscuration:	10.59	%		
Particle RI:	3.000	Absorption:	0.05	Analysis model:	General purpose	Obscuration (blue):	12.66	%
Dispersant:	Cyclohexane	Dispersant RI:	1.426			Weighted Residual:	0.774	%
Vol. Weighted Mean D[4,3]:	1.623 $\mu\text{m}$	Mode:	1.517 $\mu\text{m}$	Specific Surface Area:	4.75	$\text{m}^2/\text{g}$		
Surface Weighted Mean D[3,2]:	1.283 $\mu\text{m}$	Span:	1.406	Concentration:	0.0016	%Vol		
Result units:	Volume	Uniformity:	0.436					
$d(0.1)$ :	0.727 $\mu\text{m}$	$d(0.5)$ :	1.453 $\mu\text{m}$	$D(0.60)$ :	1.67 $\mu\text{m}$	$d(0.9)$ :	2.770 $\mu\text{m}$	



VR004, Monday, November 25, 2002 2:01:06 PM

Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %	Size ( $\mu\text{m}$ )	Vol Under %
0.010	0.00	0.105	0.00	1.058	50.53	11.462	100.00	120.269	100.00	1268.825	100.00
0.011	0.00	0.120	0.00	1.159	39.77	13.120	100.00	136.038	100.00	1465.440	100.00
0.013	0.00	0.136	0.00	1.445	49.60	15.135	100.00	158.480	100.00	1659.557	100.00
0.015	0.00	0.156	0.00	1.600	50.67	17.378	100.00	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.805	59.33	19.663	100.00	216.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.00	2.188	78.16	22.938	100.00	238.833	100.00	2511.886	100.00
0.023	0.00	0.240	0.00	2.512	85.68	23.303	100.00	275.423	100.00	2894.032	100.00
0.025	0.00	0.275	0.00	2.894	91.54	30.330	100.00	319.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.00	3.371	95.73	34.874	100.00	352.078	100.00	3801.824	100.00
0.035	0.00	0.363	0.00	3.802	98.32	39.811	100.00	418.660	100.00	4355.158	100.00
0.040	0.00	0.417	0.23	4.355	99.55	45.709	100.00	478.030	100.00	5011.672	100.00
0.045	0.00	0.479	1.10	5.072	99.97	52.481	100.00	549.541	100.00	5854.369	100.00
0.052	0.00	0.550	2.67	5.754	100.00	60.255	100.00	603.957	100.00	6608.934	100.00
0.060	0.00	0.631	5.74	6.607	100.00	69.183	100.00	724.438	100.00	7505.778	100.00
0.069	0.00	0.724	9.88	7.565	100.00	79.433	100.00	831.764	100.00	8702.595	100.00
0.079	0.00	0.820	15.46	8.710	100.00	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.925	22.37	10.000	100.00	104.713	100.00	1088.478	100.00		

Operator notes: Lebbook 273-053

Figure 23(b)

Figure 24

Stability Condition	Formulation	Assay - Initial	Rel subs (highest Indiv peak%) - Initial	Rel subs (sum of rel peaks)-Initial
Initial	Batch1 Batch2 Batch3 Batch4	ND ND 101 101	0.03 0.04 0.03 0.04	0.7 0.10 0.07 0.09
25 °C/60% RH	Formulation Batch1 Batch2 Batch3 Batch4	Assay - 1 month 99 99 99 98	Rel subs (highest Indiv peak%) - 1 month 0.04 0.06 0.05 0.05	Rel subs (sum of rel peaks) - month 0.10 0.20 0.20 0.14
40 °C/75% RH	Formulation Batch1 Batch2 Batch3 Batch4	Assay - 1 month 98 100 99 98	Rel subs (highest Indiv peak%) - 1 month 0.04 0.08 0.04 0.13	Rel subs (sum of rel peaks) - month 0.14 0.20 0.14 0.28

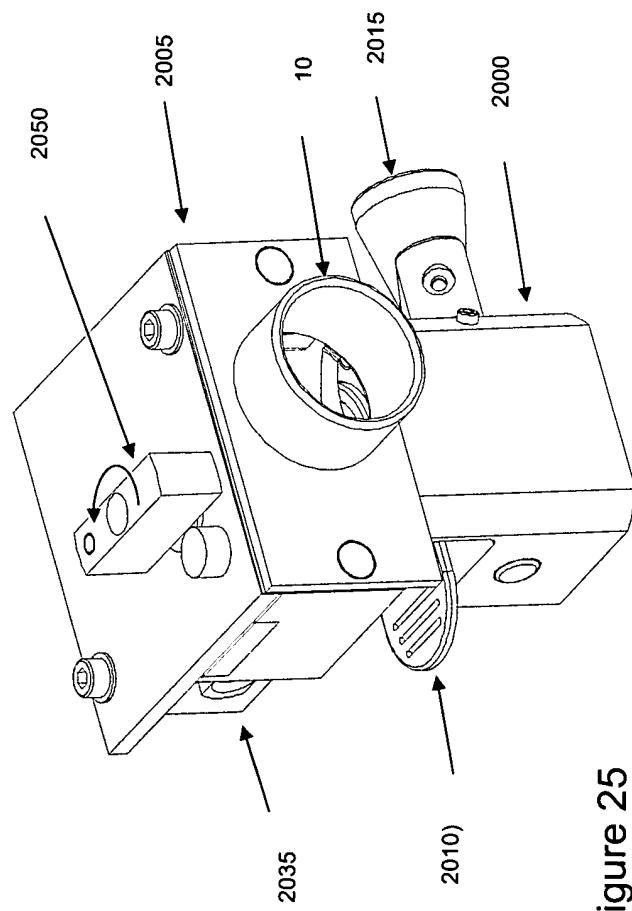


Figure 25

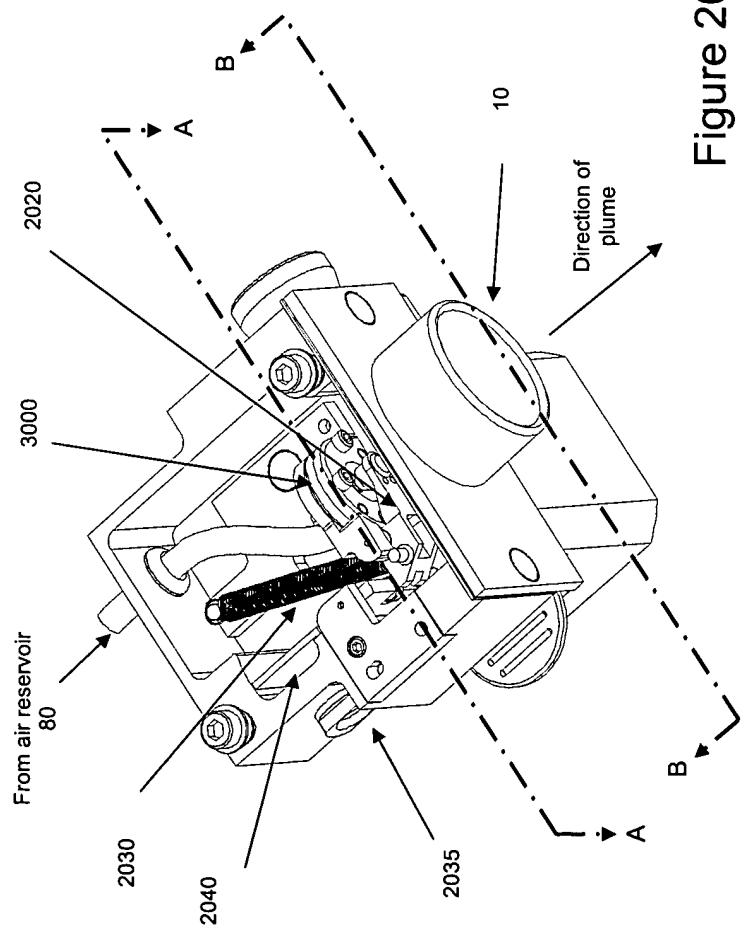
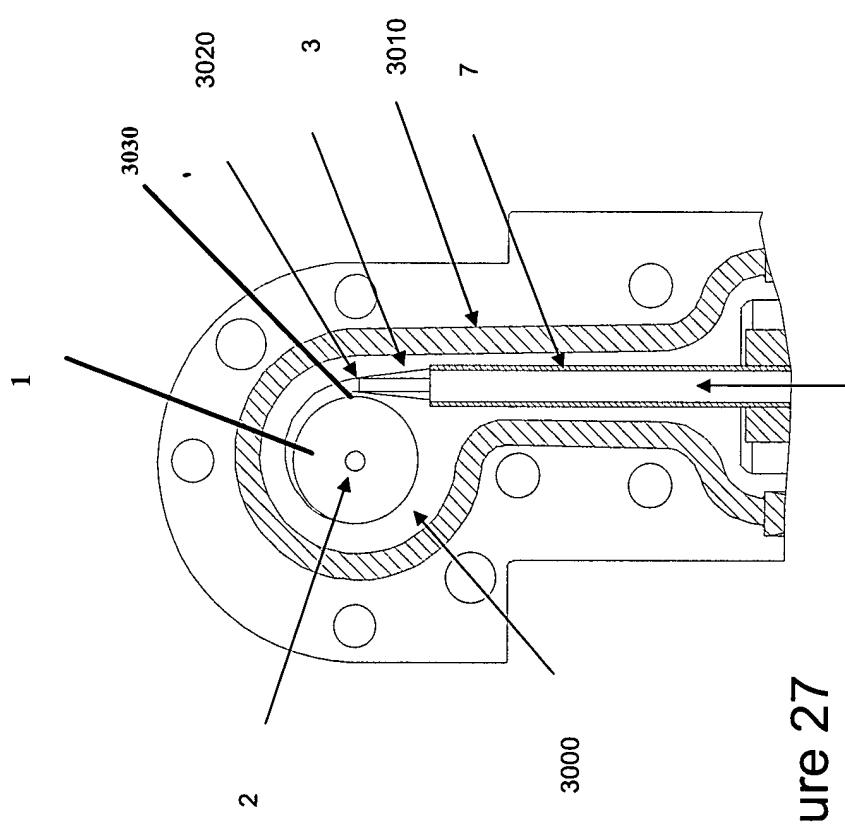


Figure 26



From drug storage blister  
(not shown)

Figure 27

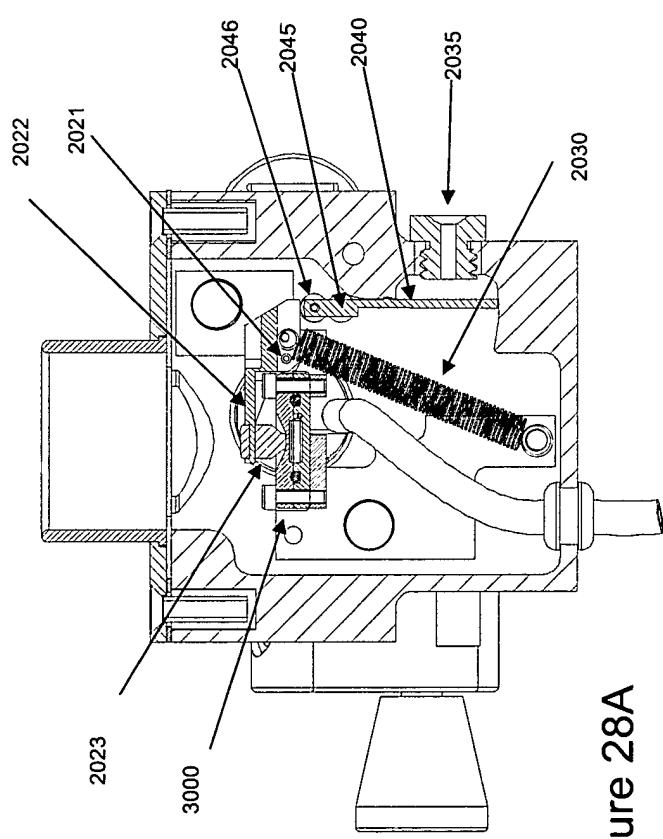


Figure 28A

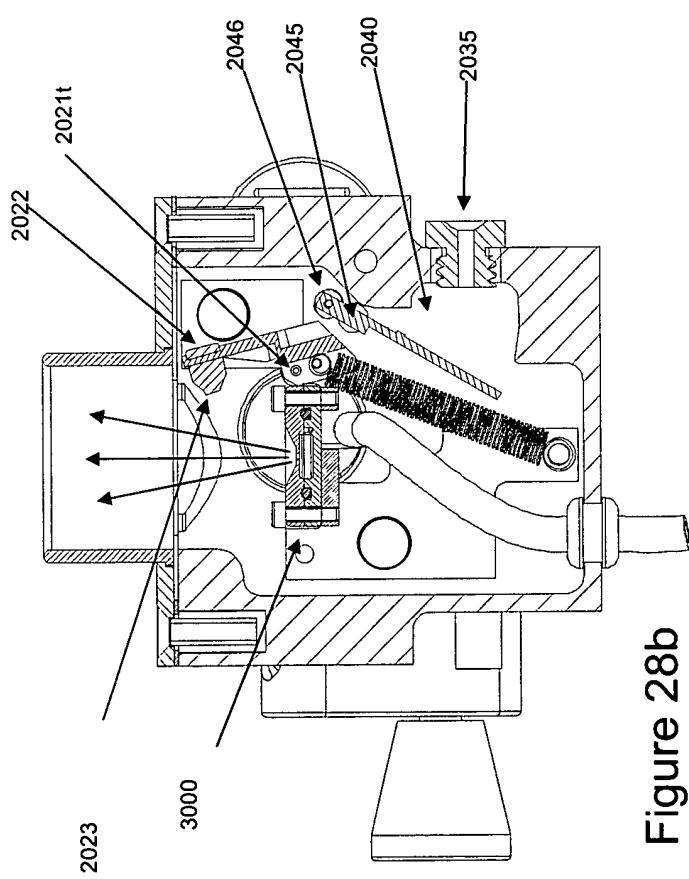


Figure 28b

Figure 29A

Formulation Details 5000	Uniformity of Delivered Dose 6000 (DUSA, n=10)				Fine Particle Performance (<5 µm Cut-Off) 7000 MSLI (ACI)											
	Drug Retention 6010		6015 DD (µg)	6020 Metered (µg)	6025 Mass Balance (%)		7005 n=		Drug Retention 7010		7015 DD (µg)	7020 FPD (µg)	7025 FPF (%)	7030 Metered	7035 Mass Balance (%)	7036 Test Flow Rate (L min <sup>-1</sup> )
	Blister (µg) 6012	Device (µg) 6013			Blister (µg) 6012	Device (µg) 6013			Blister (µg) 6012	Device (µg) 6013						
100 µg 45 - 63 µm Inversina	7.2	4.3	84	95	93	(1)	3	7.7 (7.5)	7.5 (7.2)	85 (76)	56 (52)	66 (68)	100 (91)	95 (88)	95 (95)	
100 µg 5 - 63 µm Air Jet Inversina	7.3	3.6	85	95	92	3	4.4	5.7	82	55	66	92	89	95	95	
100 µg 45-63 µm Grindomix					Not Done	3	6.9	8.6	78	39	50	93	94			
100 µg 30 - 63 µm Air Jet Grindomix					Not Done	3	5.4	6.3	86	40	47	97	96	95	95	
100 µg 45 - 63 µm Air Jet Grindomix					Not Done	3	4.2	9.4	83	52	62	97	92	95	95	
200 µg UFC020100MGA 45 - 63 µm Air Jet Inversina	10.0	5.3	188	203	96	(2)	(7.8)	(14.5)	(175)	(122)	(70)	(197)	(94)	60	60	

Figure 29B

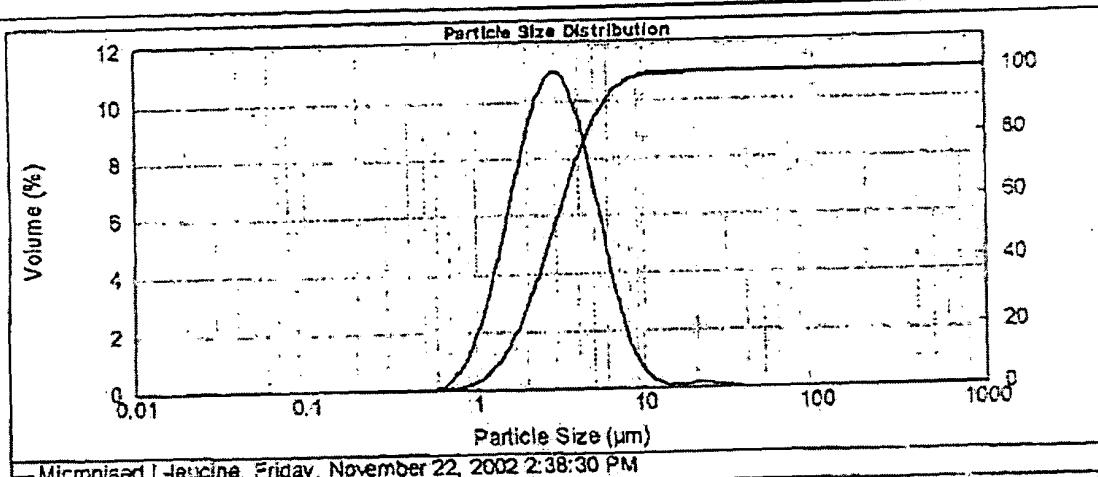
Formulation Details 5000	Uniformity of Delivered Dose 6000 (DUSA, n=11)				Fine Particle Performance (<5 µm Cut-Off) 7000 MSLI(n=2)								
	Drug Retention 6010	Delivered Dose 6015		Metered Dose 6020 (µg)	Mass Balance 6025 (%)		Drug Retention 7010		Delivered Dose 7015 (µg)	Fine Particle 7013		Metred (µg)	Mass Balance (%)
		Blister (µg) 6012	Device (µg) 6013		% nominal 6017		Blister (µg) 6012	Device (µg) 7013		FPD (µg) 7020	PPF (%) 7505		
100 µg 45 - 63 µm Inversina	6.6	7.8	81	81	95	95	8.8	5.6	82	52	64	96	96
200 µg 45 - 63 µm t Inversina	12.1	11.5	170	85	194	93	9.8	13.3	175	118	67	198	96
200 µg 45-63 µm Inversina	9.2	12.7	162	81	184	93	6.5	15.2	170	105	62	192	96
200 µg 45 - 63 µm Inversina	14.5	8.6	169	85	192	96							
200 µg 45 - 63 µm Inversina	11.0	11.2	171	85	193	95	10.7	14.1	172	117	68	196	96

Test Flow Rate = 60 L Min<sup>-1</sup>

Sample Name:  
Micronised L-leucine

Sample Source:  
Micromacinazzano  
Sample batch number:  
MMC001

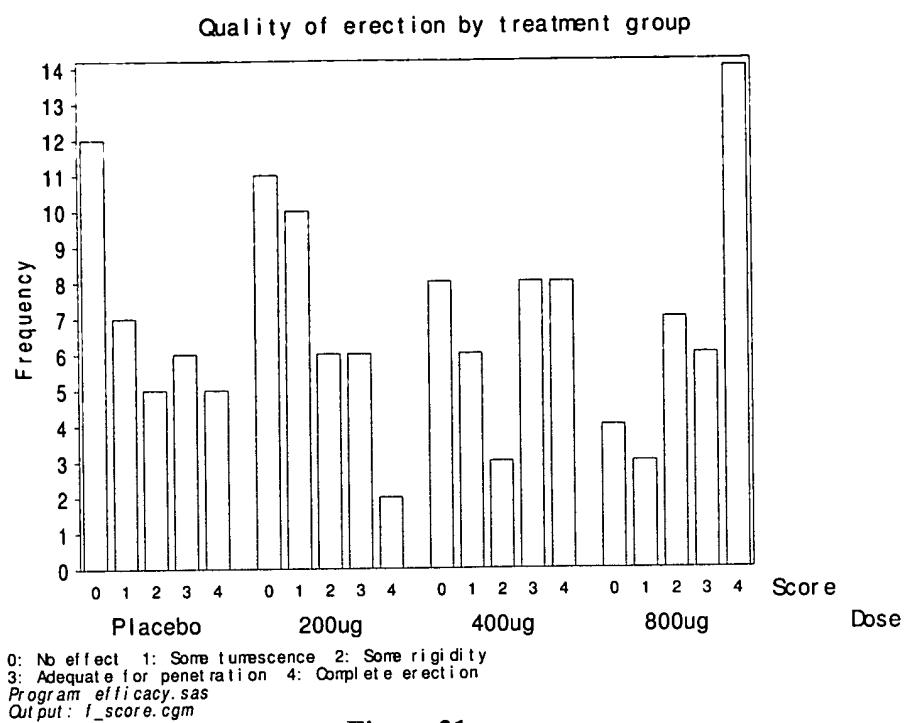
Particle Name:	Leucine	Accessory Name:	Hydro 2000SM (A)	Obscuration:	7.95	%	
Particle	1.345	Absorption:	1.5	Analysis model:	General purpose		
Dispersant:	Cyclohexane	Dispersant RI:	1.426	Obscuration (blue):	9.23	%	
				Weighted Residual:	0.422	%	
Vol. Weighted Mean D[4,3]:	3.405	µm	Mode: 2.953	µm	Specific Surface Area:	2.33	m <sup>2</sup> /g
Surface Weighted Mean D[3,2]:	2.521	µm	Span:	1.487	Concentration:	0.0025	%/Vol
Result units:	Volume		Uniformity:	0.494			
d(0.1):	1.442	µm	d(0.5):	2.905	µm	D(0.60): 3.34	µm
						d(0.9): 5.765	µm



Micronised L-leucine, Friday, November 22, 2002 2:38:30 PM

Size (µm)	Vd Under %										
0.010	0.00	0.105	0.00	1.086	3.33	11.482	99.23	120.226	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	6.09	13.183	99.38	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	10.07	15.136	99.46	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	15.46	17.378	99.54	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	22.25	19.963	99.64	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.00	2.188	30.41	22.909	99.76	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.00	2.512	39.62	26.303	99.87	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.00	2.884	49.45	30.200	99.96	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.00	3.311	59.38	34.674	100.00	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	0.00	3.802	68.85	39.811	100.00	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	0.00	4.365	77.31	45.709	100.00	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	0.00	5.012	84.41	52.481	100.00	549.541	100.00	5754.359	100.00
0.052	0.00	0.550	0.00	5.754	89.94	60.256	100.00	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	0.00	6.607	93.92	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	0.12	7.586	96.53	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	0.61	8.710	98.07	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	1.59	10.000	98.88	104.713	100.00	1036.478	100.00		

Figure 30



**Figure 31**

### Response Rate by Treatment Group

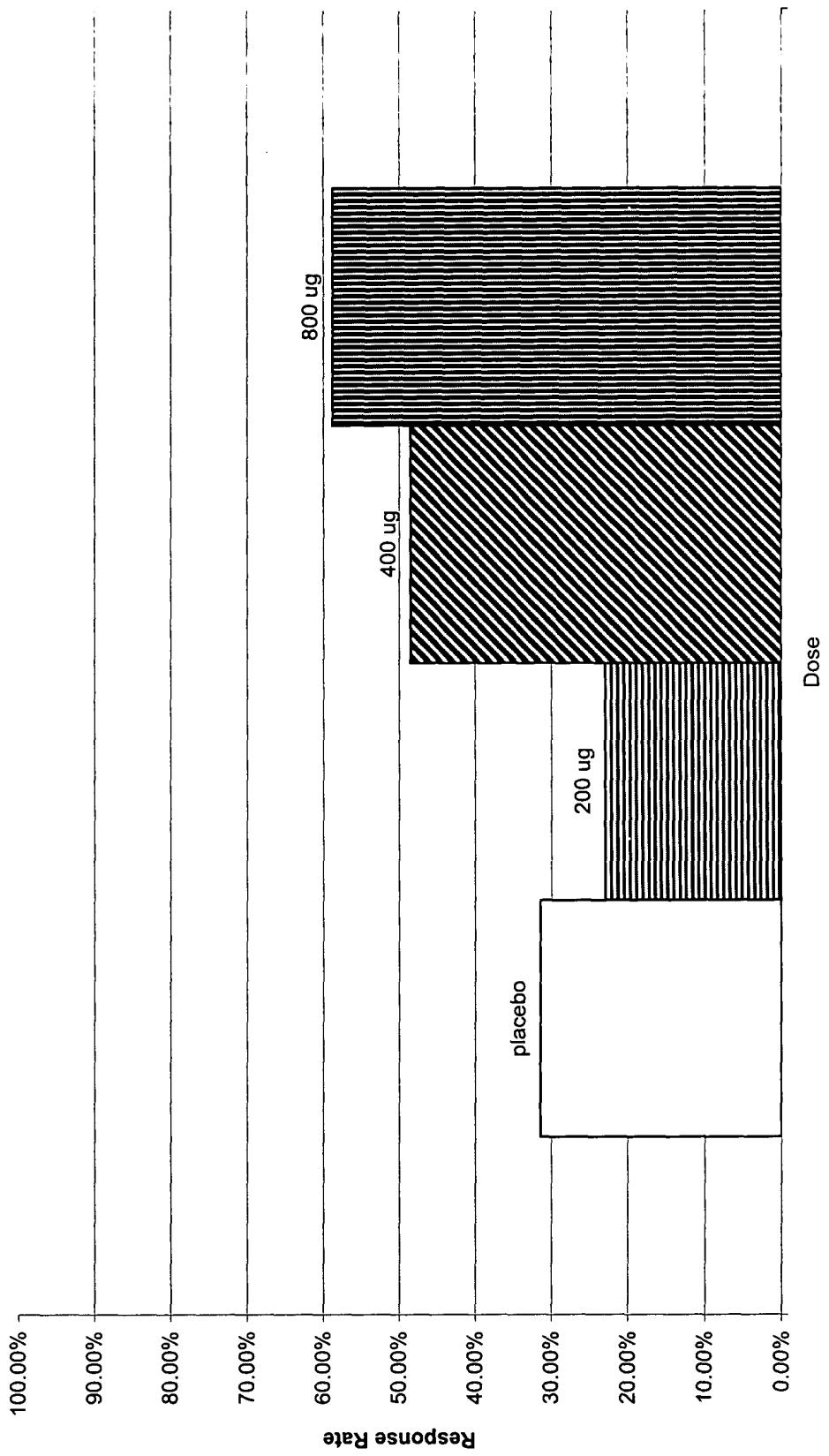
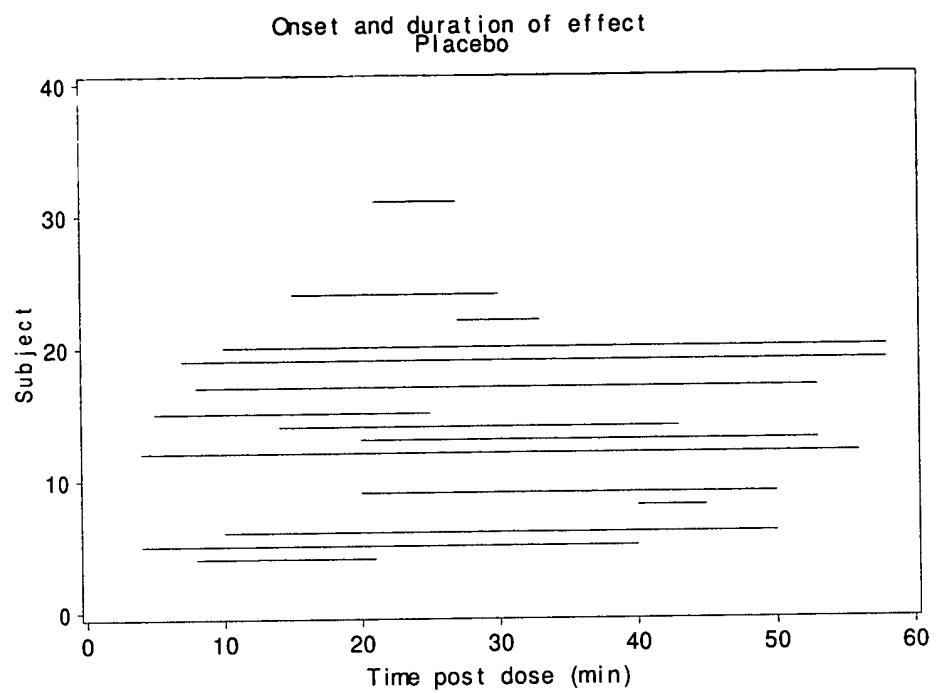
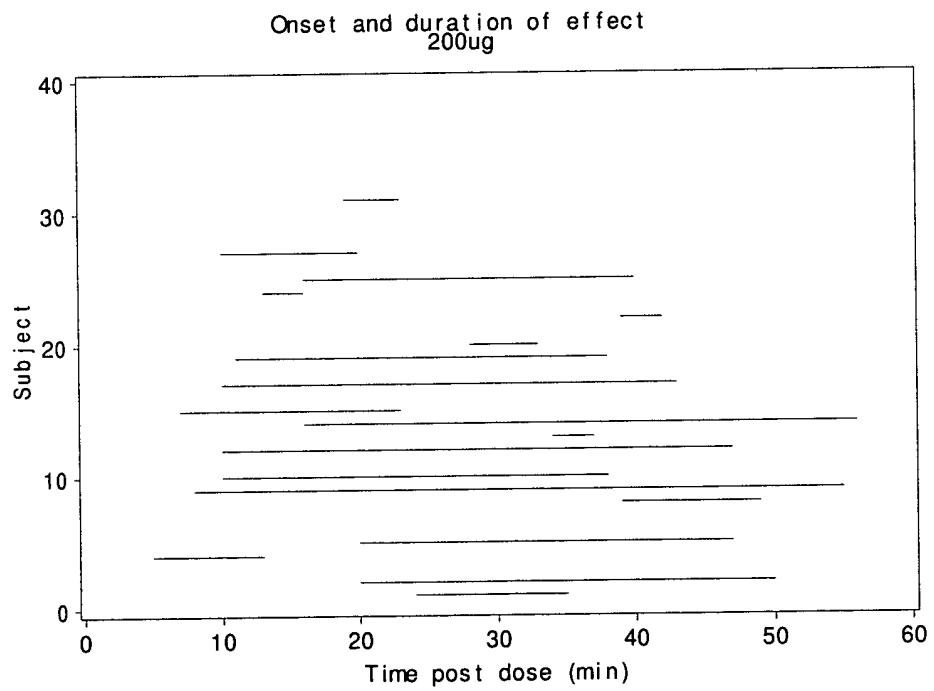


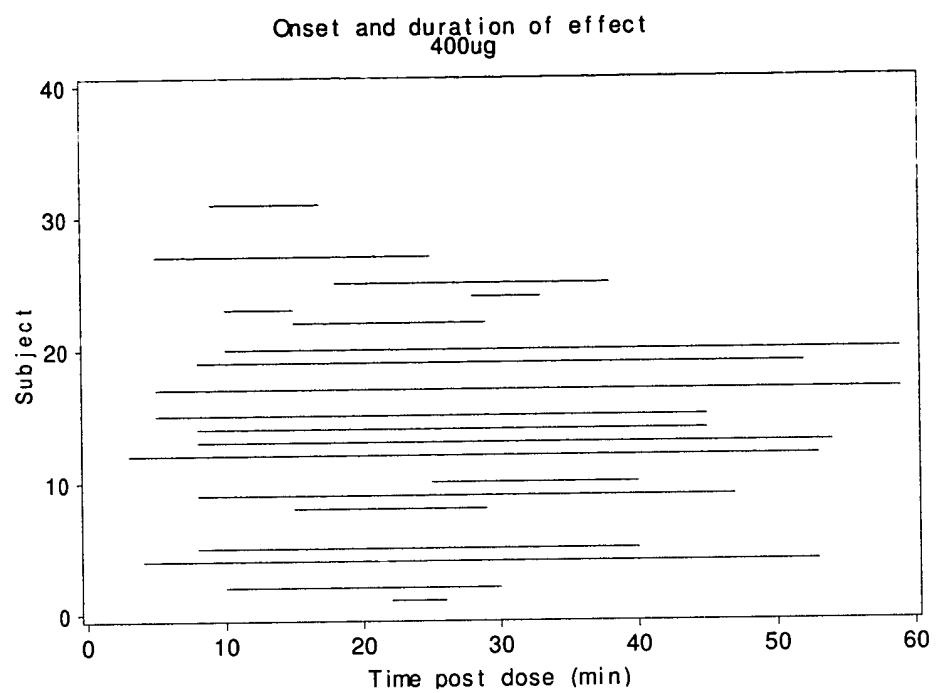
Figure 32



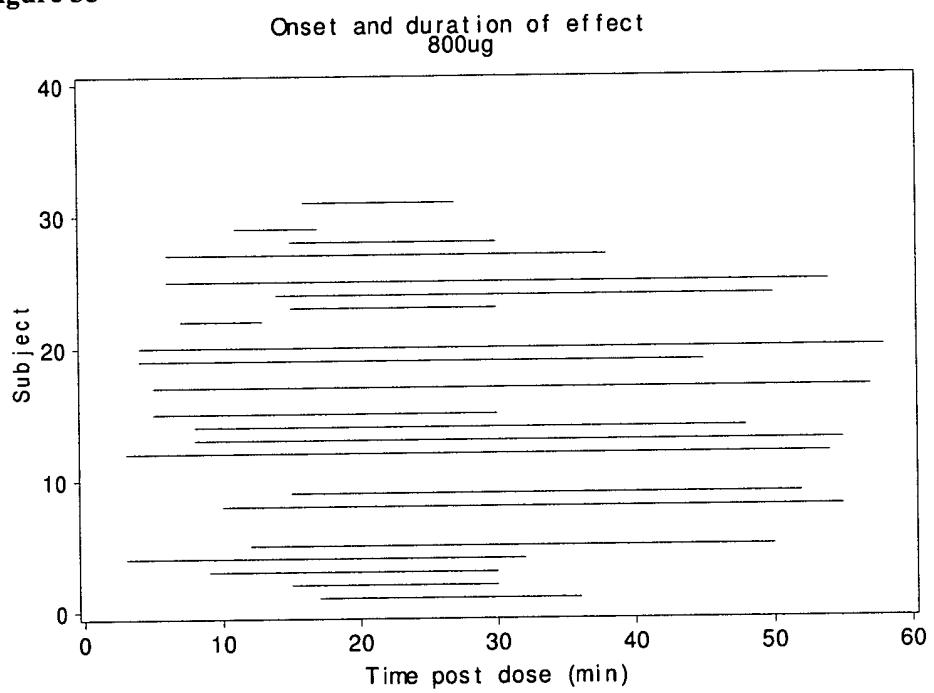
**Figure 33**



**Figure 34**

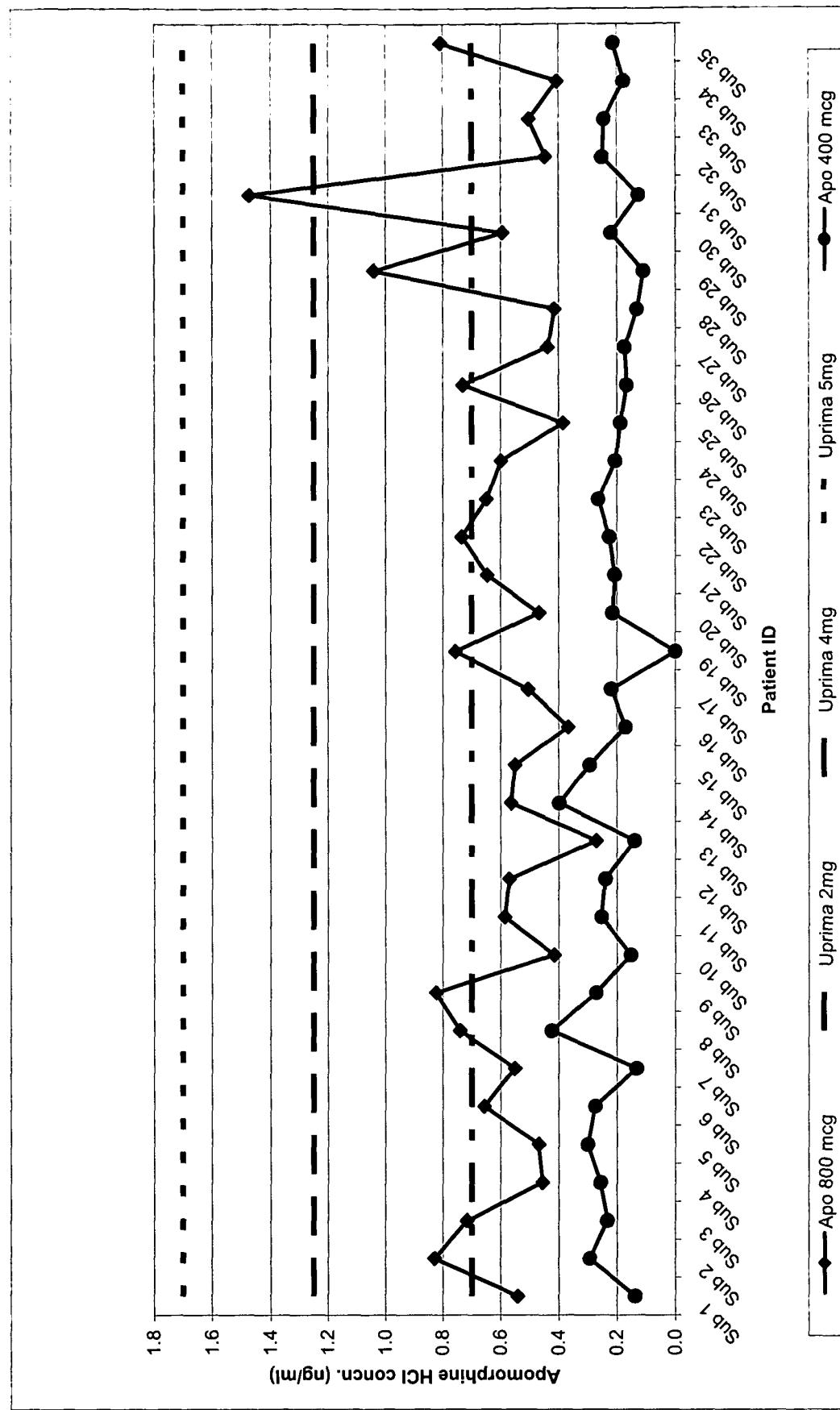


**Figure 35**

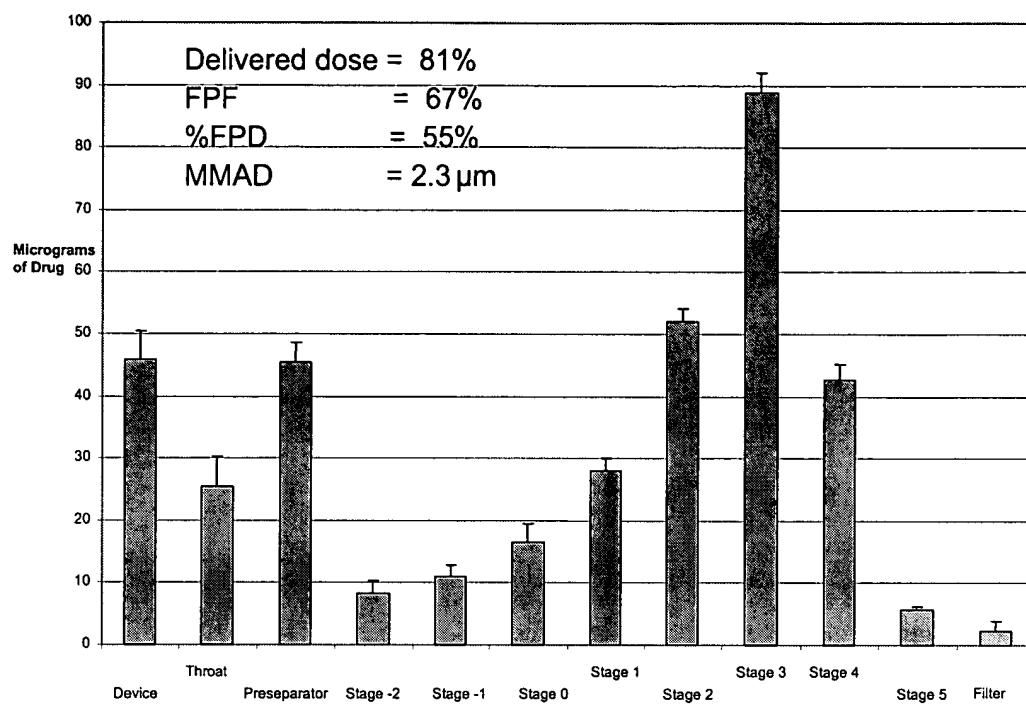


**Figure 36**

Figure 37



**Figure 38**



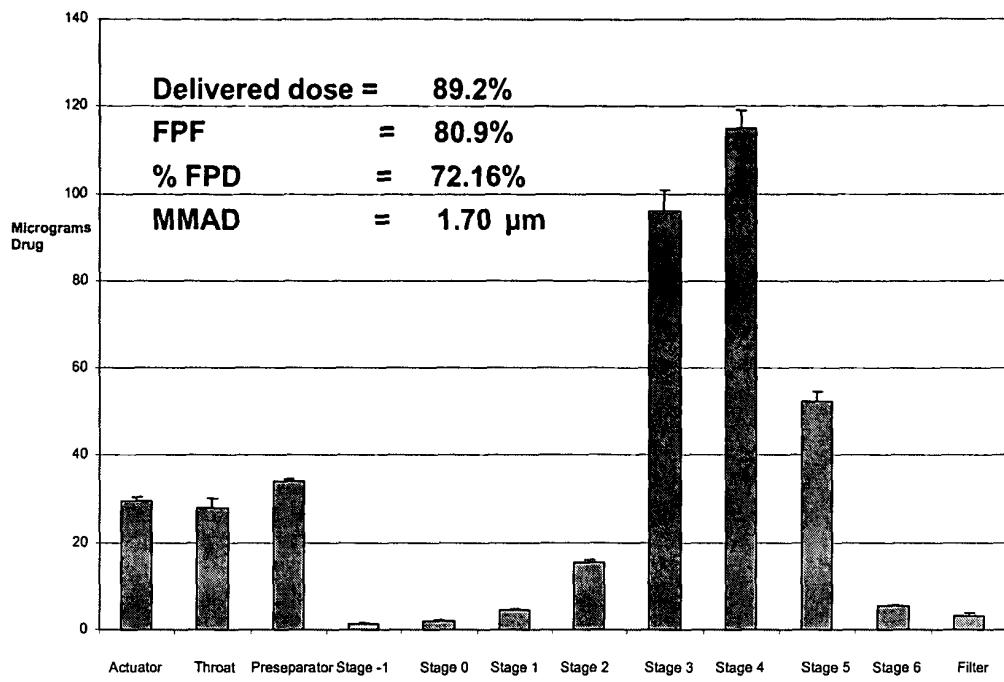


Figure 39